



## Fertility preservation and infertility treatments in breast cancer patients

**INSELSPITAL**  
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**I (M.v.W.) have nothing to declare**

## **Agenda**

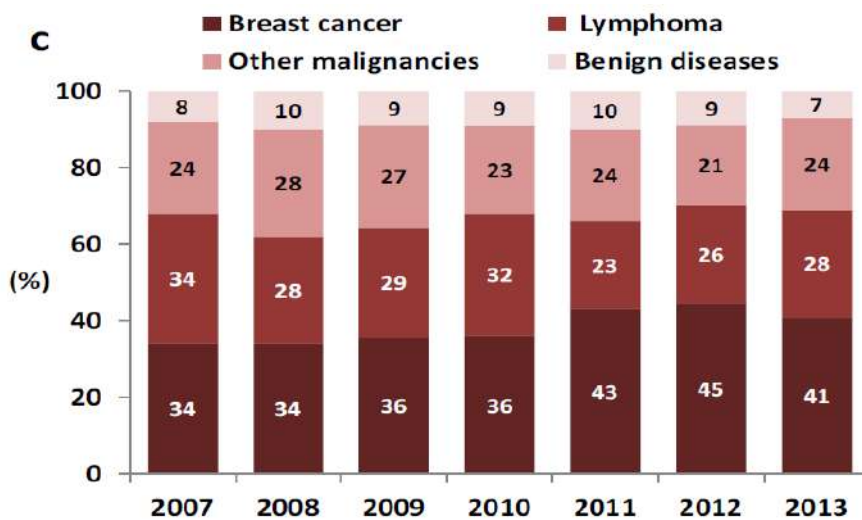
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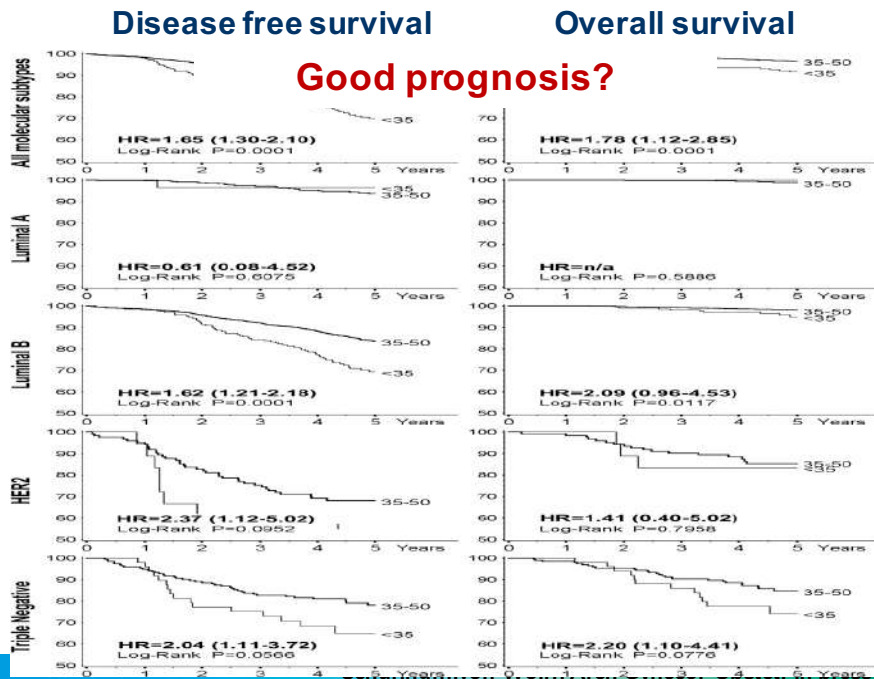
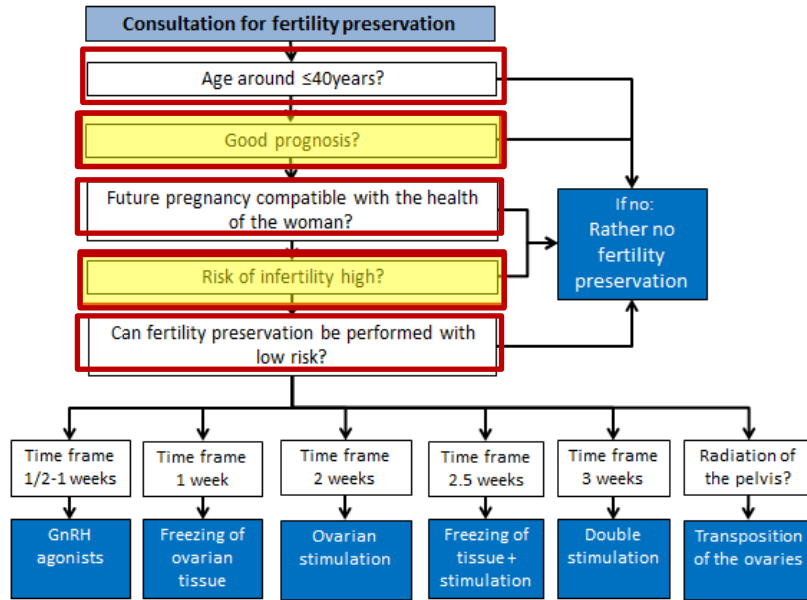
- **General remarks**
- **Fertility preservation techniques**
- **Infertility/pregnancy after breast cancer**

## Agenda

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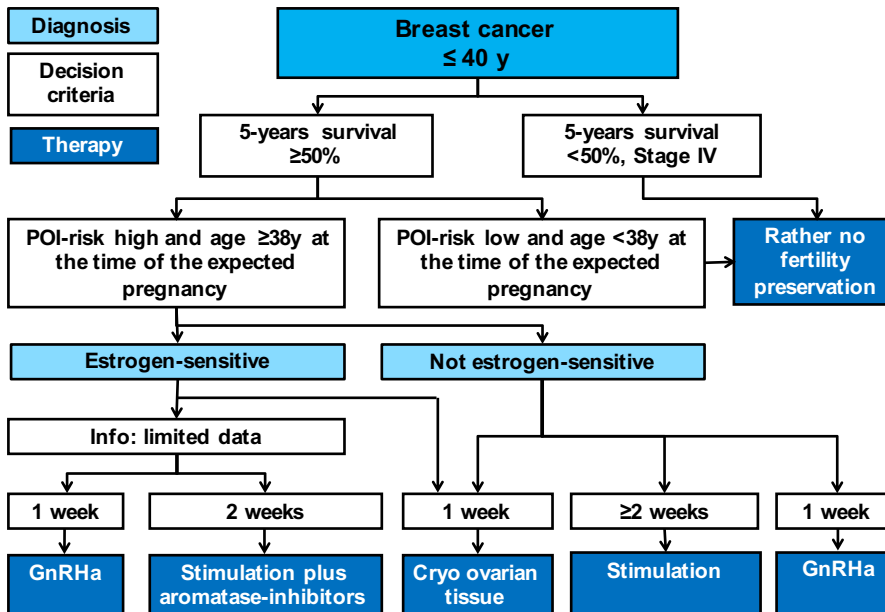
## Frequency of breast cancer counselings (>5.000 cases in *FertiPROTEKT*)





## Risk of infertility high?

Treatment Group	Ages 20-34 Years		Ages 35-39 Years		Ages ≥40 Years	
	Amenorrhoeic n/N (%)	% Resume Bleeding	Amenorrhoeic n/N (%)	% Resume Bleeding	Amenorrhoeic n/N (%)	% Resume Bleeding
<b>AC</b>						
6 mo	0/22 (0)	—	6/28 (21)	83	28/41 (68)	64
12 mo	0/27 (0)	—	2/32 (6)	50	19/49 (39)	41
24 mo	0/28 (0)	—	1/26 (4)	0	14/45 (31)	28
<b>ACT</b>						
6 mo	4/38 (11)	62	17/46 (37)	67	43/57 (75)	53
12 mo	1/36 (3)	0	8/44 (20)	38	20/56 (36)	32
24 mo	1/32 (3)	0	6/38 (16)	0	22/52 (42)	18
<b>CMF</b>						
6 mo	1/6 (17)	100	2/23 (9)	NR	22/45 (49)	16
12 mo	0/5 (0)	—	2/22 (9)	NR	20/46 (43)	12
24 mo	0/3 (0)	—	1/21 (5)	0	15/42 (36)	0



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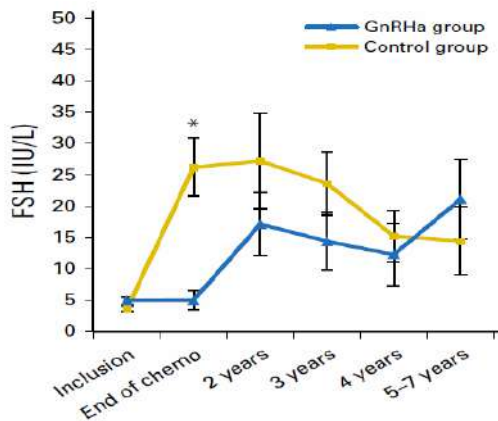
## The efficacy of GnRH agonists

### Breast cancer: Odds ratios for POI/amenorrhoea with and without GnRH agonists

Study or Subgroup	CT plus GnRHa		CT alone		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
<b>1.1.1 Breast Cancer</b>							
Badawy 2009	4	39	21	39	6.2%	0.19 [0.07, 0.50]	
Elgindy 2013	9	50	10	50	7.9%	0.90 [0.40, 2.02]	
Gerber 2011	5	30	6	30	5.4%	0.83 [0.28, 2.44]	
Karimi-Zarchi 2014	2	21	14	21	3.7%	0.14 [0.04, 0.55]	
Lambertini 2015	40	148	48	133	16.4%	0.75 [0.53, 1.06]	
Leonard 2017	12	65	23	66	11.0%	0.53 [0.29, 0.97]	
Moore 2015	5	66	15	69	6.4%	0.35 [0.13, 0.90]	
Munster 2012	3	26	2	21	2.5%	1.21 [0.22, 6.59]	
Song 2013	15	89	27	94	11.8%	0.59 [0.33, 1.03]	
Sverrisdottir 2009	14	22	18	20	16.4%	0.71 [0.50, 1.00]	
<b>Subtotal (95% CI)</b>		<b>556</b>		<b>543</b>	<b>87.6%</b>	<b>0.57 [0.43, 0.77]</b>	
Total events	109		184				
Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 16.23, df = 9 (P = 0.06); I <sup>2</sup> = 45%							
Test for overall effect: Z = 3.69 (P = 0.0002)							

## Long term efficacy of GnRH agonists

Analysis of the ovarian reserve after a chemotherapy in **hodgkins lymphoma** patient with (n=32) and without (n=35) GnRH-agonists.



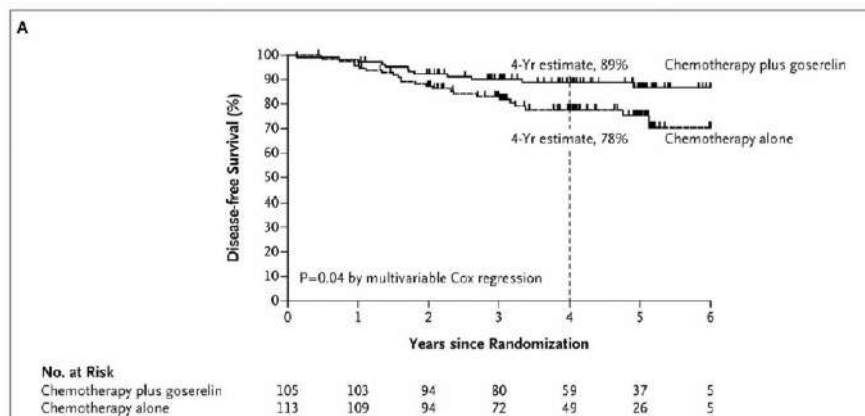
### Conclusion:

GnRHa do have a short term but possibly not a long term effect, requiring an individual decision concerning its use.

Demeestere et al.,  
J Clin Oncol, 08 2016

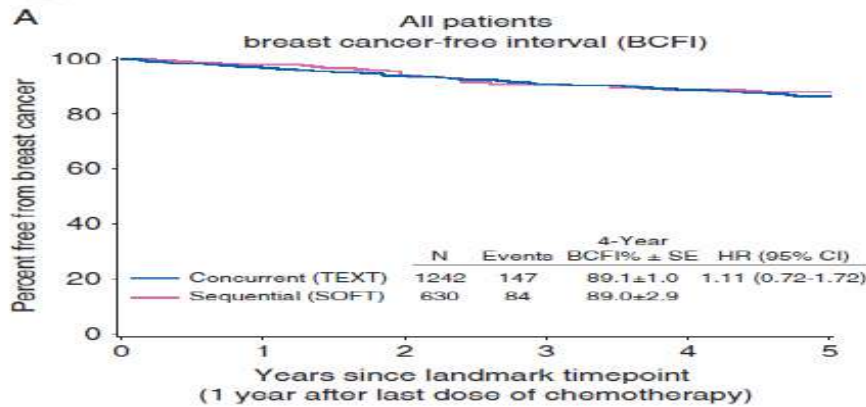
## Risk of GnRH agonists in breast cancer?

Disease free survival with vs. without GnRHa in 257 premenopausal **receptor negative** women receiving standard chemotherapy



## Risk of GnRH agonists in hormone receptor positive breast cancer?

TEXT: GnRH $\alpha$  with chemotherapy,  
SOFT: GnRH $\alpha$  after chemotherapy



## Cryopreservation of ovarian tissue

### Risk of ovarian metastasis

Study	Patients	Stage	Metastasis
Sanchez-Serrano et al. 2009 (12)	63	I: n=16 II: n=41 IIIa: n=6	<b>No</b>
Rosendahl et al. 2011 (13)	51	II/III: n=44	<b>No</b>
Hoekmann et al. 2015 (14)	23	I: n=6 II A/B: n=15 III A: n=2	<b>No</b>



## Further risks in case of tissue freezing

### Risk of ovarian metastasis increased in stage IV carcinoma:

- Lobular carcinoma: 5/14 women = 36%
- Ductal carcinoma: 2/75 women = 3%

Harris et al., Br. J. Cancer, 1994

### Up to 20% of women <35y are BRCA positive

#### Life time risk of developing ovarian cancer

- BRCA 1: 45% (2% <40y, 14% <50y)
- BRCA 2: 12% (1% <50y)

Jacobs et al., Lancet 2016

## Transplantation techniques

### Into the pelvic wall



### Into the ovary



### Onto the ovary



University women's hospital Berne

## Life birth rate following transplantation of ovarian tissue

Human Reproduction, Vol.16, No.12 pp.2838-2845, 2015  
Advanced Access publication on October 8, 2015 | doi:10.1093/humrep/dev230

human  
reproduction

ORIGINAL ARTICLE *Infertility*

### Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark

A.K. Jensen<sup>1,2</sup>, S.G. Kristensen<sup>1</sup>,  
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Hum. Reprod. Advance Access published July 4, 2016  
Human Reproduction, Vol.16, No.12 pp. 1-11, 2016  
doi:10.1093/humrep/dew143

human  
reproduction

ORIGINAL ARTICLE *Infertility*

### Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates

H. Van der Ven<sup>1,2</sup>, J. Liebenthron<sup>1,2</sup>, M. Beckmann<sup>2</sup>, B. Toth<sup>3</sup>, M. Korell<sup>4</sup>,  
J. Krüssel<sup>5</sup>, T. Frambach<sup>6</sup>, M. Kupka<sup>7</sup>, M.K. Hohl<sup>8</sup>, K. Winkler-Crepaz<sup>9</sup>,  
S. Seitz<sup>10</sup>, A. Dogan<sup>11</sup>, G. Griesinger<sup>12</sup>, F. Häberlin<sup>13</sup>, M. Henes<sup>14</sup>,  
R. Schwab<sup>15</sup>, M. Sütterlin<sup>16</sup>, M. von Wolff<sup>17,18</sup>, and R. Dittrich<sup>21</sup> on behalf  
of the FertiPROTEKT network

## Efficacy of transplantation - Life birth rate after transplantation ovarian tissue

Jensen et al., Hum Reprod 2015 (Dänemark):  
**Life birth rate/per patient 31% (incl. repeated transplant.)**

*Ferti*Protekt: van der Veen et al., Hum Reprod 2016  
**Life birth rate/per transplantation: 23%**

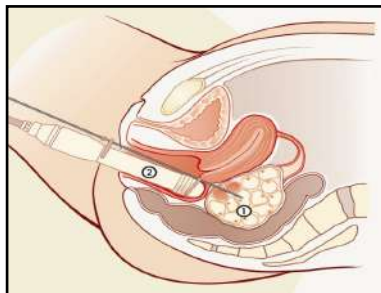
Update *Ferti*PROTEKT (updated by J. Liebenthron):  
162 transplantations in 125 women; 46 women with POI  
and follow up >12 month:  
**Life birth per 1<sup>st</sup> transplantation: 30% (plus 1 ongoing pregnancy)**

## Efficacy of transplantation – Success rate in relation to maternal age at the time of tissue freezing

49 patients (68 transplantations)	
<b>&lt;30 years</b>	
Number of patients (n)	22
Number of transplantations (n) <sup>a</sup>	32/22
Radiotherapy of the pelvis n/total (%)	2/22 (9.1)
Active tissue 1 year after transplantation n/total (%)	15/22 (68.2)
Pregnancies n/total (%)	9/22 (40.9)
Deliveries n/total (%)	6/22 (27.3)
<b>30–34 years</b>	
Number of patients (n)	14
Number of transplantations (n) <sup>a</sup>	18/14
Radiotherapy of the pelvis n/total (%)	2/14 (14.3)
Active tissue 1 year after transplantation n/total (%)	11/14 (78.6)
Pregnancies n/total (%)	5/15 (33.3)
Deliveries n/total (%)	4/14 (28.6)
<b>35–39 years</b>	
Number of patients (n)	11
Number of transplantations (n) <sup>a</sup>	13/11
Radiotherapy of the pelvis n/total (%)	0/11 (0)
Active tissue 1 year after transplantation n/total (%)	6/11 (54.5)
Pregnancies n/total (%)	2/11 (18.2)
Deliveries n/total (%)	2/11 (18.2)
<b>≥ 40 (40 and 44 years)</b>	
Number of patients (n)	2
Number of transplantations (n) <sup>a</sup>	4/2
Radiotherapy of the pelvis n/total (%)	0/2 (0)
Active tissue 1 year after transplantation n/total (%)	1/2 (50.0)
Pregnancies n/total (%)	0/2 (0)
Deliveries n/total (%)	0/2 (0)

**Best age: ≤ 35y**

## Ovarian stimulation

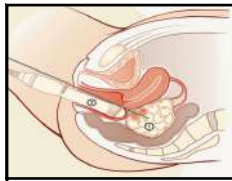


**The ovarian stimulation can be performed within 2 weeks irrespective of day of the menstrual cycle**

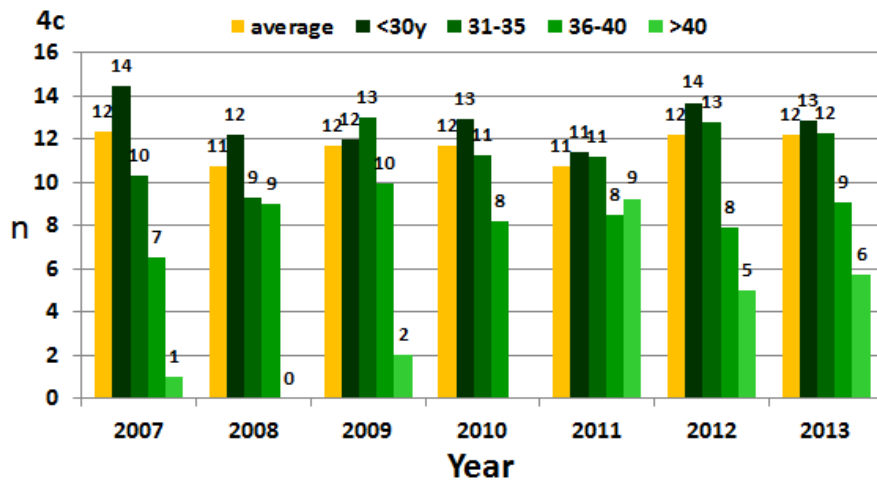
von Wolff et al., Fertil Steril, 2009  
Cakmak et al., Fertil Steril 2013  
von Wolff et al., EJOG 2016

**Risks: No relevant risks (6 out of 205 patients without a fertilized oocyte)**

Lawrenz et al., Arch Gynecol Obstet, 2011



## Collected oocytes (*FertiPROTEKT*)



## Stimulation techniques

Human Reproduction, Vol.32, No.3 pp. 568-574, 2017

Advanced Access publication on January 25, 2017 doi:10.1093/humrep/dew355

human  
reproduction

ORIGINAL ARTICLE *Infertility*

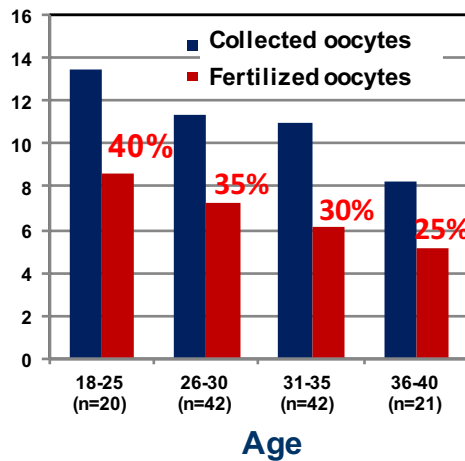
### Response to ovarian stimulation is not impacted by a breast cancer diagnosis

Molly M. Quinn\*, Hakan Cakmak, Joseph M. Letourneau, Marcelle I. Cedars, and Mitchell P. Rosen

Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco School of Medicine, San Francisco, CA 94143, USA

## Efficacy of ovarian stimulation – theoretical calculation based on the number of retrieved oocytes and registry data.

**Red numbers:** Theoretical life birth rate



Lawrenz et al.,  
2010 Fertil Steril  
v. Wolff & Dian;  
Dsch Aerzteblatt  
Int., 2011

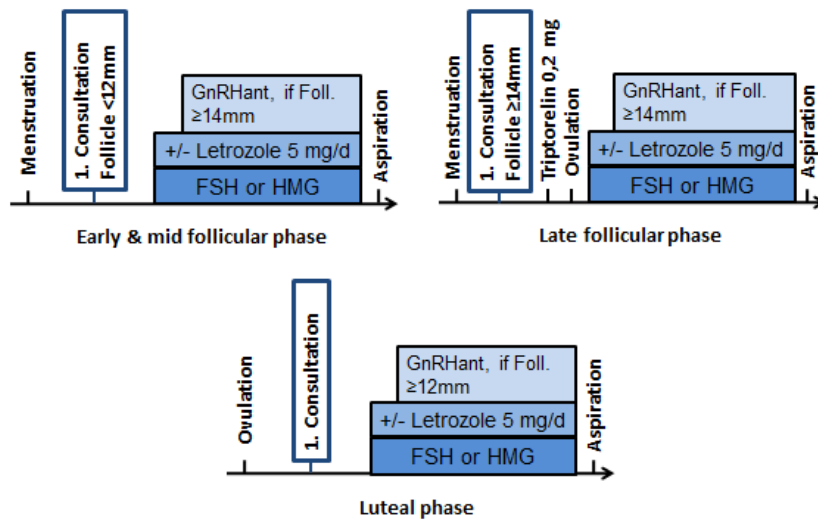
## Observational studies to calculate the Life birth rate following the use of cryopreserved oocytes and embryos

**8 studies:**

- 1203 women cryopreserved
- 90 women used their depot (7.5%)
- 196 embryo transfers
- 35 women delivered  $\geq 1$  baby  
**(Life birth rate / women: 38.9%)**
- 45 children total

Alvarez & Ramanathan,  
Hum Reprod, 2016

## Stimulation techniques



## Addition of letrozole

VOLUME 33 · NUMBER 22 · AUGUST 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

### Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer

Kutluk Oktay, Volkan Turan, Giuliano Bedoschi, Fernanda S. Pacheco, and Fred Moy

#### Conclusion

Embryo cryopreservation after ovarian stimulation with the letrozole and follicle-stimulating hormone protocol preserves fertility in women with breast cancer and results in pregnancy rates comparable to those expected in a noncancer population undergoing in vitro fertilization.

## Safety of letrozole

OPEN ACCESS Freely available online

2014 PLOS ONE

### Congenital Malformations among Babies Born Following Letrozole or Clomiphene for Infertility Treatment

Sunita Sharma<sup>1\*</sup>, Sanghamitra Ghosh<sup>1</sup>, Soma Singh<sup>1</sup>, Astha Chakravarty<sup>1</sup>, Ashalatha Ganesh<sup>2</sup>, Shweta Rajani<sup>1</sup>, B. N. Chakravarty<sup>1</sup>

**Methods and Material:** A total of 623 children born to infertile women who conceived naturally or following clomiphene citrate or letrozole treatment were included in this study. Subjects were sorted out from medical files of both mother and newborn and follow up study was done based on the information provided by parents through telephonic conversations. Babies with suspected anomaly were called and examined by specialists for the presence of major and minor congenital malformations. Other outcomes like multiple pregnancy rate and birth weight were also studied.

**Results:** Overall, congenital malformations, chromosomal abnormalities were found in 5 out of 171 (2.9%) babies in natural conception group and 5 out of 201 babies in the letrozole group (2.5%) and in 10 of 251 babies in the CC group (3.9%).

**Conclusions:** There was no significant difference in the overall rate of congenital malformations among children born to mothers who conceived naturally or after letrozole or CC treatment.

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## Influence of pregnancy on the prognosis

### Lymph node negative

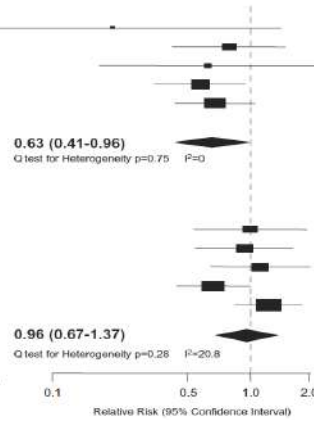
	if No. of participants	
	Non-pregnant	Pregnant
Cooper, 1970	1/16	10/34
Ariel, 1989	7/30	180/600
Lehaby, 1996	2/10	88/207
Mueller, 2003	16/136	152/901
Kroman, 2008	18/107	1150/4887
<b>Subtotal PRR (95% CI)</b>	<b>44/300</b>	<b>1570/6629</b>

### Lymph node positive

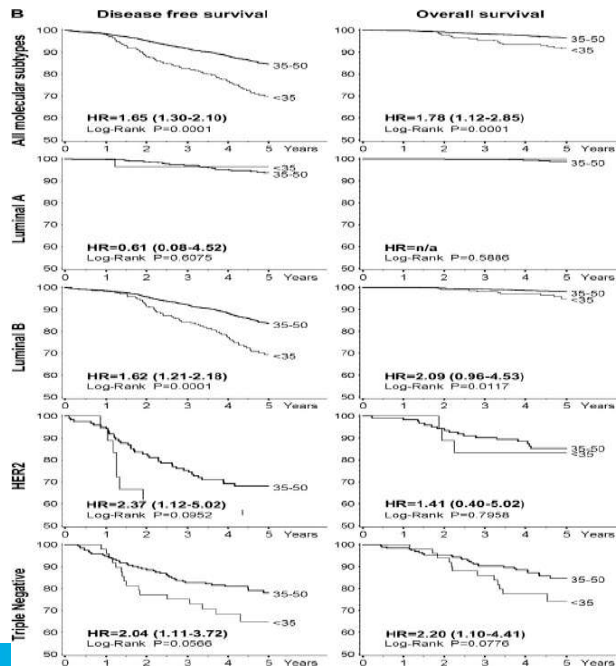
	if No. of participants	
	Non-pregnant	Pregnant
Cooper, 1970	8/11	12/22
Ariel, 1989	7/16	141/300
Lehaby, 1996	3/4	85/127
Mueller, 2003	25/77	220/550
Kroman, 2008	26/61	1976/4631
<b>Subtotal PRR (95% CI)</b>	<b>67/169</b>	<b>2434/5630</b>

Between-strata Heterogeneity: Meta-regression P-value=0.09

### Survival rate



**But.....**



Cancello et al.,  
Ann Oncol 2010



## Infertility treatments

**In which cases is the risk of relapse lower after hormone dependant breast cancer? (Estimated success rates):**

**High ovarian reserve:**

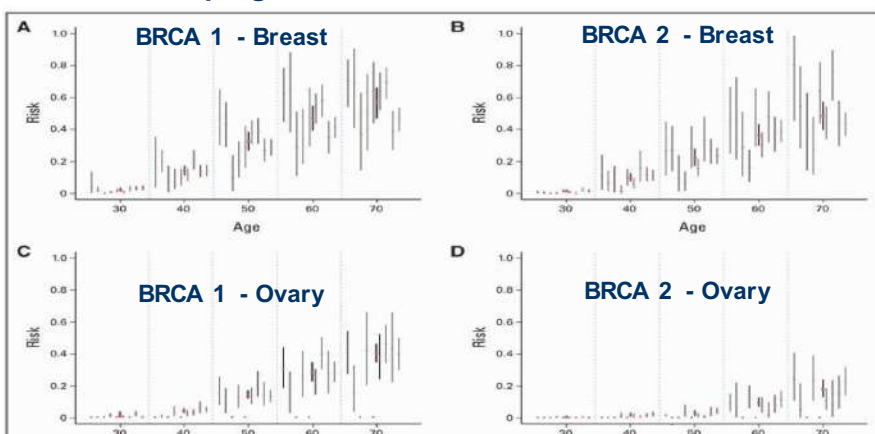
- 3 month treatment by IUI: Live birth rate 20%
- 3 month treatment by NC-IVF: Live birth rate 30%
- 3 month treatment by IVF: Live birth rate 60%

**Low ovarian reserve:**

- 3 month treatment by IUI: Live birth rate 20%
- 3 month treatment by NC-IVF: Live birth rate 30%
- 3 month treatment by IVF: Live birth rate 30%
- E2 increasing medications should only be used if necessary
- IVF: co-treatment with E2-reducing medications (Tam, letrozole) is useful

## Is PGD a solution in case of BRCA mutation?

**Risk of developing cancer in BRCA carriers in different studies**



BRCA mutations follows *autosomal dominant inheritance* pattern: Polar body and embryo biopsy are both possible

## Summary

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- **Breast cancer treatment causes a low risk of infertility at young age but a high risk at high age, especially due to long lasting endocrine treatment.**
- **GnRHa can also be applied in hormone dependant breast cancer.**
- **In women <35y both ovarian tissue freezing and ovarian stimulation are possible options.**
- **In women >35y ovarian stimulation might be more effective.**
- **Pregnancy need to be permitted by oncologists and risk of relapse should be very low.**
- **Infertility treatment: Short «Time to pregnancy» counts possibly more than gonadotropin free treatments.**